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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,248	09/30/2003	Peter K. Rogan	33026	5913

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/16/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/676,248	ROGAN ET AL.	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33,43-52 and 54* is/are pending in the application.

4a) Of the above claim(s) *1-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-52 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/27/2010 has been entered.

Response to Amendment

2. The declaration by Mauricio Miralles under 37 CFR 1.132 filed 11/24/2010 is sufficient to overcome the rejection of claims 43-52 and 54 based upon Knight and Boyle.

Formal matters and Claim status

This action is in response to claims filed 11/24/2010 and the arguments filed 10/27/2010 and 11/24/2010

Claims 1-33 are withdrawn.

Claims 34-42 are canceled.

Claims 43-52 and 54 are under consideration.

The objection to the specification due to the discrepancies between the table and sequence listing has been withdrawn.

The 103 based on Knight and Boyle in view of the amendment and the declaration under 1.132.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 43-53 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43, recites, "single copy hybridization probes of known human DNA sequences." Claim 49 recites, "said single copy probe being comprised of human DNA." The response of 10/27/2010 asserts that BAC, PAC and P1 clones are non-human DNA. Thus the metes and bounds of the claim are unclear based on this assertion. One of skill in the art realizes that human DNA or human DNA sequences can be cloned into vectors (plasmids, BAC, YAC, PAC, and P1 clone). The claims are drawn to comprising language and thus allow for additional elements. Further the arguments appear to imply that the claims are limited to only human DNA for the probes. Based on this logic, DNA amplified by PCR would not be human DNA as it is not directly obtained from a human cell, but amplified from a human cell and comprises human DNA sequences. Thus the scope of "human DNA" and "human DNA sequences" are unclear in view of the arguments. The metes and bounds of "human DNA" and "human DNA sequences" should be placed on the record to clarify this issue. If applicant intends the claims to require only "DNA from human cells" by the terminology, applicant should provide specific support in the specification. Further applicant should demonstrate how the claims are enabled for such a limited interpretation of the language as the specification provides for amplification of human

DNA sequences, which based on the narrow interpretation implied by the response is not human DNA, but in vitro amplified human DNA sequences.

Claim Rejections - 35 USC § 103-New Grounds

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 43, 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knight et al (Am. J. Human Genetics (2000) volume 67, pages 320-332) in view of Rogan et al (Genome Research (2001) volume 11, pages 1086-1094).

The claims are drawn to a method of detecting cytogenetic abnormalities in an individual comprising screening at least one chromosome by hybridization of a plurality of single copy hybridization probes of known human DNA sequences, each of said

single copy probes being 25 bp to about 15 kb in length, causing said single copy probes to hybridize to at least one chromosome of the human said hybridization occurring with 600kb of the terminal nucleotide of at least one chromosome and detecting hybridization patterns of said single copy probes, said hybridization patterns indicating cytogenetic abnormalities when present. The claim only requires the detection of cytogenetic abnormalities if present.

With regards to claim 43, Knight et al teaches a method of fluorescence in situ hybridization (FISH) on interphase chromosomes (see page 322, 1st column). Knight et al teaches the probes were labeled and detected. Knight et al teaches the probes and the distance from the telomere (terminal nucleotide) in table 1. Knight teaches the distance from the terminal nucleic acid was as little as 268-296 kb for 6ptel48 and teaches sequencing of the probes (see page 322, 2nd column, 1st paragraph). Knight thus teaches method of detecting cytogenetic abnormalities with a plurality of probes within 600 kb of the terminal nucleotide of the chromosome by screening at least one chromosome by hybridization with probes of known sequences, and detecting cytogenetic abnormalities when present. Knight teaches the probes were synthesized by Nick translation. Nick translation results in probes between 2 and 5 kb in length.

With regards to claim 45, Knight teaches that 60 + probes did not cross hybridize (see tables 1 and 3).

With regards to claim 46, Knight teaches the probes had known sequences as demonstrated by the primers of table 2.

With regards to claim 47, Knight teaches the probes were nick translated. Nick translation results in a plurality of short probes of between 50 bp and 12 kb.

Knight teaches the use of FISH, interphase FISH and Fiber FISH for screening of probes.

Knight does not specifically teach the use of probes of 50 bases to 12 kb.

However, Rogan teaches, "We describe a method to design and produce custom genomic probes from computationally defined, single-copy genomic sequences. Probe sequences are inferred from DNA sequences of larger genomic intervals of interest with software that determines the locations of repetitive DNA elements contained in these sequences. By excluding the repetitive sequences, probes are designed from 2-kb to 10-kb single-copy (sc) intervals, synthesized in vitro, purified, and detected by FISH to chromosomes (scFISH). We developed scFISH probes from several chromosomal regions. This approach streamlines the development and production of single-copy, sequence-specific hybridization probes for detection of genetic rearrangements in both rare and common chromosome anomalies" (1086).

Rogan teaches, "scFISH and cloned genomic probes differ in a number of respects. Aside from the absence of repetitive DNA, scFISH probes are enriched for expressed sequences because the genomic intervals from which they were derived are presumed to contain genes implicated in specific disorders. These probes usually contain coding and noncoding sequences, but occasionally consist entirely of single-copy, unexpressed sequence intervals (i.e., the 4100-bp and 2290-bp probes

from the *MAGEL2* locus).Additionally, scFISH probes can be quickly designed and produced by long PCR. Propagation of conventional FISH probes prepared by recombinant DNA techniques is slower, especially when library screening is taken into account. The sequence content of scFISH probes is precisely defined, in contrast with unsequenced cloned probes that are commonly used for FISH. Cloned probes may, in some instances, detect low-copy complex repetitive sequence families, which participate in a variety of recurrent chromosomal rearrangements, producing additional signals from hybridization to other related loci. To ensure that FISH probes detect unique sequences, scFISH probe sequences are verified by BLAST analysis. To visualize an individual member of a low copy complex repeat family, however, scFISH probes can be prepared with PCR primers designed to uniquely amplify a specific element (i.e., containing weakly conserved regions of the repeat) and washed at high stringency after hybridization. Based on our analyses of chromosomes 21q and 22q and on the comprehensive state of the genome sequence, it should be feasible to develop scFISH probes for molecular analysis of most euchromatic chromosomal rearrangements. Adequate resolution can be obtained with probes 2 kb in length to detect chromosome breakpoints and gene(s) disrupted by such rearrangements, as has been previously performed by Southern hybridization and occasionally by fiber-FISH, neither of which preserves higher-order chromosome structure. By expanding the repertoire of probes available for molecular genetic analysis of chromosomal alterations, probes can be developed to delineate multigene family members, identify and size marker chromosomes, and detect uncommon chromosome abnormalities that could not

otherwise be studied (because commercial or research probes are not available). scFISH will also find application in chromosomal analysis of other organisms for which comprehensive catalogs of repetitive sequences have been compiled and genomic sequences of sufficient length are available." (1092).

The sequences of Rogan's probes are known as exemplified by his teachings of accession numbers (see table1).

Rogan teaches his probes are between 2 kb and 10kb (see page 1086, lines 4-9).

Therefore it would have been prima face obvious to one of ordinary skill in the art at the time the invention was made to improve the fluorescent in situ hybridization method of Knight by the use of single copy probes taught by Rogan. The artisan would be motivated as Rogan teaches the single copy probes are quicker to design and reproduce. The artisan would further be motivated as Rogan suggests the single copy probes can be used to detect uncommon chromosomal abnormalities in organisms in which genomic sequences are known. The artisan would have a reasonable expectation of success as Rogan suggest his method of probe design can be performed on any organism in which repetitive and genomic sequences are known.

Response to arguments

The response of 10/27/2010 asserts that the teachings of Knight are not human DNA but are from BACs, PACs and P1 clones. This argument has been thoroughly reviewed but is not found persuasive as the claims are drawn to human DNA sequences. The DNA sequence of the vectors of Knight are cloned human sequences.

Thus these arguments are not persuasive. Further the instant rejection are drawn to the combination of Rogan and Knight. Rogan teaches methods of producing single copy probes by amplification of known human sequences.

The response of 11/24/2010 also traverses the instant rejection. The response relies upon the declaration of Mauricio Miralles. The declaration indicates Miralles has a masters degree in molecular biology and provides arguments about the ability to amplify a nucleic acid sequence based on a GenBank accession number or primer. The declaration with respect to GenBank accession numbers, primers and amplification are not relevant to any of the rejections of record and thus are not considered. The declaration continues by presenting arguments to repetitive sequences such as CoT in the sequence of Knight (a). These arguments have been thoroughly reviewed but are not considered persuasive as Rogan teaches methods of designing probes to known sequences to eliminate the repetitive sequences.

The declaration further asserts that it is impossible to get a single copy probe (without repeat sequences) that will cover 100kb. This argument has been thoroughly reviewed but is not considered persuasive as the claims are not drawn to sequences without repeat sequences but single copy probes. If applicant's intend to assert that no repeat sequences can be in the probes, then the claims should be amended to present such a limitation. However, it is noted SEQ ID NO 84 presents 3 CCC repeat sequences. Thus this argument upon close examination of the instant specification may result in an enablement and/or written description rejection. The response continues by asserting, " When we analyzed the adjacent sequences of the STS and expanded up or

down stream up to 100 Kb, it is impossible to get a single copy probe (without repeat sequences) that will cover 100 Kb. Fig 1 below shows the location and sequences of clone GS-62-L8. When the sequence is expanded only 10 times (1.2 Kb region) our analysis showed repeat sequences less than 500 bp on either side." This argument has been thoroughly reviewed but is not considered persuasive as the rejection is not based on solely the teachings of Knight, but both Knight and Rogan. The teachings of Rogan specifically address how to eliminate repetitive sequences. Further response has not indicated the repeat sequences found were actually in the probe, but merely indicate they are on either side and addressed previously the claims do not exclude the presence of repeat sequences. Further a nucleic acid sequence can be unique or a single copy probe and have repetitive, as SEQ ID NO 84 appears to be despite having multiple CCC repeats.

The conclusion with respect to Knight in view of Boyle are moot in view of the new grounds of rejection.

Thus the arguments are not persuasive in view of the new grounds of rejection.

8. Claims 44, 48, 49-52, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knight et al (A) (Am. J. Human Genetics (2000) volume 67, pages 320-332) Rogan et al (Genome Research (2001) volume 11, pages 1086-1094). n view of Knight (b) (Journal of Medical Genetics (2000) volume 37, pages 401-409).

This rejection is consistent with the scope of claim 49 requiring human DNA sequences.

The teachings of Knight (A) and Rogan are set forth above.

However, Knight (B) et al teaches, "Chromosomal rearrangements involving the ends of chromosomes (telomeres) are emerging as an important cause of human genetic diseases. This review describes the development of first and second generation sets of telomere specific clones, together with advances in fluorescence in situ hybridization (FISH) technology, which have made the prospect of screening for telomeric rearrangements a realistic goal. Initial FISH studies using the telomere specific clones indicate that they will be a valuable diagnostic tool for the investigation of mental retardation, the characterization of known abnormalities detected by conventional cytogenetic analysis, spontaneous recurrent miscarriages, infertility, hematological malignancies, and preimplantation diagnosis, as well as other fields of clinical interest. In addition, they may help investigate telomere structure and function and can be used in the identification of dosage sensitive genes involved in human genetic disease.(see abstract). Knight et al further teaches, "The results suggested that at least 6% of idiopathic mental retardation might be explained by submicroscopic rearrangements involving telomeres. If true, then subtelomeric rearrangements could be the second most common cause of mental retardation after Down's syndrome. Therefore, it was important to extend these studies to include all possible telomeres and a larger sample set." Knight (b) further teaches, "The first method, the use of DNA polymorphisms, requires DNA samples from the child and both parents. When both parents are heterozygous and share no alleles, a rearrangement in the child can be inferred from the presence of only a single allele (a deletion) or the presence of three alleles (a trisomy). This technique has the advantage of being able to detect isodisomy

(the inheritance of two chromosome homologues from one parent), but it is limited by the degree of polymorphism of the marker and by the need to have access to samples from both parents. Indeed, marker informativity must be very high for this technique to be efficient."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of cytogenetic analysis and probes taught by Knight (A) and Rogan to associate specific hybridization patterns with clinical abnormalities as taught by Knight (b), because Knight (B) teaches it would allow for better understanding of the clinical abnormalities. Knight (b) specifically teaches the such methods can be used to better understand the causes of idiopathic mental retardation and/or cancers. It would have further been prima facie obvious to compare the sequences to standard genetic maps as Knight (B) teaches comparison of hybridization of children to parents (standard genetic maps). The artisan would have a reasonable expectation of success as Knight(A) and Knight (B) both teach method of detecting polymorphisms by FISH.

Response to Arguments

The response of 10/27/2010 and the response and declaration of 11/24/2010 present the same arguments previous addressed with respect to Knight and Rogan. The response further asserts the claim requires "human DNA." This argument has been thoroughly reviewed but is not considered persuasive as the claims are drawn to "probes comprised of human DNA" which encompasses additional elements such as vector sequences and encompasses the use of human DNA sequences in the absence

of a limiting definition of "human DNA." These arguments are not persuasive for the reasons of record.

Summary

No claims are allowed over prior art cited.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven C Pohnert/
Primary Examiner, Art Unit 1634